

08/25/00

jc872 U.S. PTO

# UTILITY PATENT APPLICATION TRANSMITTAL (Large Entity)

(Only for new nonprovisional applications under 37 CFR 1.53(b))

Docket No.  
388A

Total Pages in this Submission

**TO THE ASSISTANT COMMISSIONER FOR PATENTS**Box Patent Application  
Washington, D.C. 20231

Transmitted herewith for filing under 35 U.S.C. 111(a) and 37 C.F.R. 1.53(b) is a new utility patent application for an invention entitled:

**COMBINATION PREPARATION FOR CONTRACEPTION BASED ON NATURAL ESTROGENS**

and invented by:

**Michael DITTGEN, Sabine FRICKE, Herbert HOFFMANN, Claudia MOORE, Michael OETTEL, Monika OSTERTAG**jc862 U.S. PTO  
09/648858

08/25/00

If a **CONTINUATION APPLICATION**, check appropriate box and supply the requisite information:☒ **Continuation** ☐ **Divisional** ☐ **Continuation-in-part (CIP)** of prior application No.: 08/738,314

Which is a:

☐ **Continuation** ☐ **Divisional** ☐ **Continuation-in-part (CIP)** of prior application No.: \_\_\_\_\_

Which is a:

☐ **Continuation** ☐ **Divisional** ☐ **Continuation-in-part (CIP)** of prior application No.: \_\_\_\_\_

Enclosed are:

**Application Elements**

1. ☒ Filing fee as calculated and transmitted as described below
2. ☒ Specification having 20 pages and including the following:
  - a. ☒ Descriptive Title of the Invention
  - b. ☐ Cross References to Related Applications (if applicable)
  - c. ☐ Statement Regarding Federally-sponsored Research/Development (if applicable)
  - d. ☐ Reference to Microfiche Appendix (if applicable)
  - e. ☒ Background of the Invention
  - f. ☒ Brief Summary of the Invention
  - g. ☒ Brief Description of the Drawings (if drawings filed)
  - h. ☒ Detailed Description
  - i. ☒ Claim(s) as Classified Below
  - j. ☒ Abstract of the Disclosure

# UTILITY PATENT APPLICATION TRANSMITTAL (Large Entity)

(Only for new nonprovisional applications under 37 CFR 1.53(b))

Docket No.  
388A

Total Pages in this Submission

## Application Elements (Continued)

3. ☐ Drawing(s) (when necessary as prescribed by 35 USC 113)
- a. ☐ Formal                      Number of Sheets \_\_\_\_\_
- b. ☐ Informal                      Number of Sheets \_\_\_\_\_
4. ☒ Oath or Declaration
- a. ☐ Newly executed (original or copy)                      ☐ Unexecuted
- b. ☒ Copy from a prior application (37 CFR 1.63(d)) (for continuation/divisional application only)
- c. ☒ With Power of Attorney                      ☐ Without Power of Attorney
- d. ☐ DELETION OF INVENTOR(S)  
Signed statement attached deleting inventor(s) named in the prior application,  
see 37 C.F.R. 1.63(d)(2) and 1.33(b).
5. ☒ Incorporation By Reference (usable if Box 4b is checked)  
The entire disclosure of the prior application, from which a copy of the oath or declaration is supplied  
under Box 4b, is considered as being part of the disclosure of the accompanying application and is hereby  
incorporated by reference therein.
6. ☐ Computer Program in Microfiche (Appendix)
7. ☐ Nucleotide and/or Amino Acid Sequence Submission (if applicable, all must be included)
- a. ☐ Paper Copy
- b. ☐ Computer Readable Copy (identical to computer copy)
- c. ☐ Statement Verifying Identical Paper and Computer Readable Copy

## Accompanying Application Parts

8. ☐ Assignment Papers (cover sheet & document(s))
9. ☐ 37 CFR 3.73(B) Statement (when there is an assignee)
10. ☐ English Translation Document (if applicable)
11. ☐ Information Disclosure Statement/PTO-1449                      ☐ Copies of IDS Citations
12. ☒ Preliminary Amendment
13. ☒ Acknowledgment postcard
14. ☒ Certificate of Mailing
- ☐ First Class                      ☒ Express Mail (Specify Label No.): EK 957561458 US

# UTILITY PATENT APPLICATION TRANSMITTAL (Large Entity)

(Only for new nonprovisional applications under 37 CFR 1.53(b))

Docket No.  
388A

Total Pages in this Submission

## Accompanying Application Parts (Continued)

15. ☐ Certified Copy of Priority Document(s) (if foreign priority is claimed)

16. ☐ Additional Enclosures (please identify below):

## Fee Calculation and Transmittal

### CLAIMS AS FILED

For	#Filed	#Allowed	#Extra	Rate	Fee
Total Claims	7	- 20 =	0	x \$18.00	\$0.00
Indep. Claims	2	- 3 =	0	x \$78.00	\$0.00
Multiple Dependent Claims (check if applicable) <input type="checkbox"/>					\$0.00
BASIC FEE					\$690.00
OTHER FEE (specify purpose) _____					
TOTAL FILING FEE					\$690.00

- ☐ A check in the amount of \_\_\_\_\_ to cover the filing fee is enclosed.
- ☒ The Commissioner is hereby authorized to charge and credit Deposit Account No. 19-4675 as described below. A duplicate copy of this sheet is enclosed.
- ☒ Charge the amount of \$690.00 as filing fee.
  - ☒ Credit any overpayment.
  - ☒ Charge any additional filing fees required under 37 C.F.R. 1.16 and 1.17.
  - ☐ Charge the issue fee set in 37 C.F.R. 1.18 at the mailing of the Notice of Allowance, pursuant to 37 C.F.R. 1.311(b).

  
Signature

Dated: AUGUST 25, 2000

cc:

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

**Examiner:**

**Art Unit:**

**In RE:**        **New Continuation Application of Michael DITTGEN, et al,  
                      filed under 37 C.F.R. 1.53**

**Ser. No.:**     **Continuation of Ser. No. 08/738,314**

**Filed:**        **Simultaneously**

**PRELIMINARY AMENDMENT**

Hon.Commissioner of Patents  
and Trademarks,

Washington, D. C. 20231

Sir:

In advance of Examination on the merits, please make the following  
changes and consider the following REMARKS:



consists of 13 to 17 of said second stage daily dosage portions and said second stage daily dosage portions each include more of said at least one synthetic or natural gestogen in said second group than in said first group; and

wherein said effective amount of said at least one natural estrogen is constant in said first stage and also constant in said third stage but said effective amount in said third stage is smaller than said effective amount in said first stage.

9. The combination preparation as defined in claim 8, wherein said at least one natural estrogen is selected from the group consisting of estradiol, estradiol compounds metabolized to said estradiol in the body, conjugated equine estrogens and phytoestrogens and said at least one natural or synthetic gestogen is selected from the group consisting of natural progesterone and synthetic gestogens.

10. The combination preparation as defined in claim 8, wherein said at least one natural estrogen is selected from the group consisting of estradiol, conjugated equine estradiol and estradiol valerate and said at least one natural or synthetic gestogen is selected from the group consisting of desogestrel, medoxyprogesterone acetate and dienogest.

11. The combination preparation as defined in claim 8, wherein said second stage daily dosage portions each include from 1.5 to 3 times more of said at least

one synthetic or natural gestogen in said second group than in said first group of said second stage.

12. A method of contraception, said method comprising the steps of:

a) administering from 2 to 4 first stage daily dosage portions each consisting of an effective amount of at least one natural estrogen in a first stage of the method;

b) after step a), administering a first group of 3 to 5 second stage daily dosage portions each consisting of a first effective amount of a combination of said at least one natural estrogen and at least one natural or synthetic gestogen in a second stage of the method;

c) after step b), administering a second group of 13 to 17 second stage daily dosage portions each consisting of a second effective amount of said combination of said at least one natural estrogen and said at least one natural or synthetic gestogen in the second stage of the method;

d) after step c), administering from 2 to 4 third stage daily dosage portions each consisting of an effective amount of said at least one natural estrogen in a third stage; and

e) after step d), administering in an additional stage consisting of from 2 to 4 additional stage daily dosage portions each consisting of a pharmaceutically acceptable placebo;

wherein said second effective amount of said combination in said second group of said second stage includes more of said at least one synthetic or

natural gestogen than said first effective amount of said combination in said first group; and

wherein said effective amount of said at least one natural estrogen is constant in said first stage and also constant in said third stage, but said effective amount of said at least one natural estrogen is smaller in said third stage than in said first stage.

13. The method as defined in claim 12, wherein said at least one natural estrogen is selected from the group consisting of estradiol, estradiol compounds metabolized to said estradiol in the body, conjugated equine estrogens and phytoestrogens and said at least one natural or synthetic gestogen is selected from the group consisting of natural progesterone and synthetic gestogens.

14. The combination preparation as defined in claim 12, wherein said at least one natural estrogen is selected from the group consisting of estradiol, conjugated equine estradiol and estradiol valerate and said at least one natural or synthetic gestogen is selected from the group consisting of desogestrel, medoxyprogesterone acetate and dienogest.



## REMARKS

This application is a continuation of copending U.S. Patent Application, Ser. No. 08/738,314 (the parent), which has now been allowed.

The owner of the above-identified U.S. Patent Application wants to keep a U.S. Patent Application pending for the subject matter of the present application, despite the fact that the parent application has been allowed.

The more limited claims 8 to 14 that were filed during the prosecution of the parent application have been filed by means of this preliminary amendment. The broadest claims 1 to 7 have not been canceled.

Should the Examiner require or consider it advisable that the specification, claims and/or drawing be further amended or corrected in formal respects to put this case in condition for final allowance, then it is requested that such amendments or corrections be carried out by Examiner's Amendment and the case passed to issue. Any costs involved should be charged to the deposit account of the undersigned (No. 19-4675). Alternatively, should the Examiner feel that a personal discussion might be helpful in advancing the case to allowance, he or she is invited to telephone the undersigned at 1-631-549 4700.

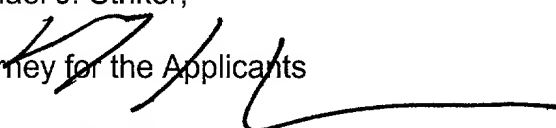
In view of the foregoing, favorable allowance is respectfully solicited.

Respectfully submitted,

Michael J. Striker,

Attorney for the Applicants

Reg. No. 27,233

A handwritten signature in black ink, appearing to read 'MJ Striker', is written over the text 'Attorney for the Applicants'.

0054380" 2332450

0055290" 95584960

BE IT KNOWN that WE, Michael DITTGEN, Sabine FRICKE, Herbert HOFFMANN, Claudia MOORE, Michael OETTEL and Monika OSTERTAG, citizens of Germany, whose post office addresses are, respectively, Heidenberg 35/37, Apolda, Germany 99510; An der Riese 16, Jena, Germany 07749; Treunertstrasse 12, Jena, Germany 07749; Novalisstrasse 23, Jena, Germany 07747; Beethovenstrasse 30, Jena, Germany 07743; Haussenstrasse 14, Göttingen, Germany 37073, have invented a certain new and useful

**COMBINATION PREPARATION FOR CONTRACEPTION**

**BASED ON NATURAL ESTROGENS**

of which the following is a complete specification thereof:

## Background of the Invention

The present invention relates to a multistage contraceptive preparation based on natural estrogens.

Oral contraceptives were first marketed 60 years ago. By continuous research it has been possible to reduce the required dosages of hormones in a stepwise manner. Currently low dosage oral contraceptives exist which chiefly comprise an estrogen component and a gestogen component. The hormone dosage of these contraceptives is delivered in different combinations and dosages in the form of combination preparations (one-stage preparation) or multistage combination preparations (staged preparations) and sequenced preparations (two-stage preparations) over time periods of from 21 to 28 days.

One-stage preparations (usually designated as combination preparations) are characterized by a constant dosage of certain estrogens and gestogens each day. Because of the uniform delivery of gestogen ingredients with estrogen components from the first application day, the combination preparation is a highly reliable contraceptive.

The ovulatory LH-peak is reliably suppressed with all forms of combination preparation so that both ovulation and Corpus luteum formation are suppressed (M. Elstein, et al, "Studies on low dose oral contraceptives: cervical mucus and plasma hormone changes in relation to circulating

d-nogestrel and 17-ethinyl estradiol concentrations", in Fertil Steril. 27, p. 892, 1976; Kontrazeption mit Hormonen (trans: Contraception with Hormones), H. D. Taubert and H. Kuhl, eds., Georg Thieme Verlag, Stuttgart/New York, 1965). Of course early secretion changes of the still weakly developing endometrium can cause intervening bleeding above all in the first cycle under the influence of a gestogen.

Modified combination or multistage preparations currently include two-stage preparations and three-stage preparations. Two-stage preparations are those, which contain a gestogen dosage, which is reduced in comparison to the conventional combination preparation, which is increased in the second stage (cycle half). A stage with a lowered gestogen dosage lasting for 11 days follows in a 21/22 day pill regime, while the estrogen dosage remains the same over the administration period.

Three-stage preparations contain lowered gestogen dosages as well as lowered estrogen dosages in the first delivery stage, which increases in two stages to its highest gestogen dosage in the last 7 to 10 days, while the estrogen ingredient is increased either uniformly or briefly during the middle of the cycle over a duration of 5 to 6 days analogously to the normal physiological cycle. Three-stage preparations allow the entire dosage of gestogens to be maintained at a lower level than in other oral contraceptives (L. Carlborg, "Comparison of contraceptive

acceptability of levonorgestrel and ethinyl oestradiol administered in a three-stage (trionetta) and a one-stage (neoletta) version", in Contraception 27, p. 5, 1983).

Two-staged preparations (sequenced preparations) contain a pure estrogen component in the first 7 to maximum 11 days of use and additionally a gestogen ingredient in the following 10 to 14 days. Because of that the endometrium is subjected to changes which very closely correspond to the normal physiological cycle. They therefore provide very good cycle control. Sequence preparations lower the basal gonadotropin level in a manner similar to combination preparations, in which the FSH-level is more strongly suppressed or lowered than the LH-level (K.AKTORIES, et al, "Die Beeinflussung des Ovarialzyklus durch verschiedene Typen hormonaler Kontrazeptiva (trans: The effect of different types of hormonal contraceptives on ovarian cycles)" in Geburtshilfe Frauenheilkunde 36, P. 318, 1976).

All currently known combination preparations for oral\_\_contraception contain ethinyl estradiol or its 3-methyl ester, mestranol, as estrogen ingredient. The latter compound is a prodrug and is metabolized in the body to ethinyl estradiol. Ethinyl estradiol has, among other things, a series of disadvantages and side effects. This synthetic estrogen is rapidly resorbed in the stomach and intestinal tract, however, because it is easily metabolized, it is rapidly absorbed already in the mucous membrane of the

005390 8384950

small intestine and/or rapidly changes chemically as a result. Besides this process has large individual variations. Hence unsatisfactory and large individual differences of bioavailability of ethinyl estradiol result. Ethinyl estradiol causes suicidal blockage of the Cytochrome P-450 system (F.P.Guengerich, "Oxidation of alpha-ethinyl estradiol by human liver Cytochrome P-450", in Molec. Pharmacol. 33, p.500, 1988; R. Bocker, et al, "In vitro interaction of contraceptive steroids with human liver Cytochrome P-450 enzymes, Advances Contraception 7, p.140, 1991) and inhibits its own metabolism. Since gestogens and a series of other foreign materials/medications in large part are converted by the same decomposition paths, the repeated application of ethinyl estradiol-containing contraceptives can lead to an accumulation of certain xenobiotics in the body. Furthermore ethinyl estradiol has carcinogenic properties (B.T.Zhu, et al, "The carcinogenic activity of ethinyl estrogens is determined by both their hormonal characteristics and their conversion to catechol metabolites" in Endocrinol. 132, p. 577, 1993).

The general administration of natural estrogens is suggested as an alternative to ethinyl estradiol in German Patent Applications DE 41 04 385 and DE 42 24 534.

A contraceptive administration system is known from U.S.Patent 4,921,843, in which a placebo is taken between

the last day's dosage of the second component and the first day's dosage of the first component. This contraceptive administration system has the disadvantage that follicle maturation begins during the administration of the placebos.

The sole administration of natural estrogens has currently not found a practical application. Thus H.D. Taubert and H. Kuhl (Kontrazeption mit Hormonen, H.D. Taubert and H. Kuhl, Eds., Georg Thieme Verlag, Stuttgart, New York, 1995) fail to suggest the use of natural estradiols as estrogen ingredients in oral contraceptives. While the gestogen ingredients alone provide a reliable contraceptive protection, the proliferation of the endometrium by the natural estrogen is insufficient. A bleeding anomaly such as intervening bleeding results up to the blood-free cycles.

Up to now difficulties have occurred in experiments to develop a so-called "semi-natural pill" based on natural estrogens (e.g. micronized 17 $\beta$ -estradiol, natural 17 $\beta$ -estradiol esters, conjugated estrogens, phytoestrogens and estrone, estriol and their derivatives). For example the combination of estradiol (estradiol valerate 1 mg and/or 2 mg administered for 10 and/or 11 days) and cyproterone acetate ( 1 mg and/or 2 mg for 10 to 11 days) caused 33 % intervening bleeding (E. HIRVONEN, et al, in "Oral Contraceptive-containing natural estradiol for premenopausal women", in Maturitas **21**, p. 27, 1995) or the combination of



estradiol (3 mg) and desogestrel (0.150 mg) for 21 days caused 30 % intervening bleeding (H. Coelingh Bennink, "Research in Contraception", 10th Congress of the European Association of Gynecologists and Obstetricians, 1995).

Preliminary experiments for the instant invention were performed with constant estradiol dosages over 28 days and constant gestogen dosages over 24 days as well as with different estradiol dosages (2.0 mg, 4.0 mg and 2.0 mg over 7, 14 and 7 days respectively) and constant gestogen dosages over 21 days. These studies failed because the intervening bleeding rate of 25 % was not substantially different from that already known from the studies of E. Hirvonen and H. Coelingh Bennink (E. Schleussner, Jenapharm GmbH Report, 1995).

#### **Summary of the Invention**

It is an object of the present invention to provide a hormonal contraceptive whose administration substantially improves cycle bleeding behavior, maintains the contraceptive action of the estrogen/gestogen combination and minimizes or prevents undesirable side effects (carcinogenic activity and accumulation of xenobiotics).

According to the invention the multistage combination preparation for contraception comprises from 2 to 4 first stage daily dosage portions each including an effective amount of at least one natural estrogen as sole active ingredient, from 16 to 22 second stage daily dosage portions each including an effective amount of a combination of at least one natural estrogen and at least one natural or synthetic gestogen as active ingredient; from 2 to 4 third stage daily dosage portions each including an effective amount of at least one natural estrogen as sole active ingredient; and from 2 to 4 final stage daily dosage portions each containing a pharmaceutically acceptable placebo.

In a preferred embodiment of the invention the second stage daily dosage portions are divided into a first group consisting of 3 to 5 daily dosage portions and a second group consisting of 13 to 17 daily dosage portions. The gestogen content of the individual daily dosage portions of the second group is higher than that of the individual daily dosage portions of the first group. Advantageously the gestogen content of the individual portions of the second group amounts to 1.5 to 3 times the gestogen content of the individual portions of the first group. The total number of the administered daily dosages is advantageously 28. Above all estradiols, such as 17 $\beta$ -estradiol, estradiol compounds such as 17 $\beta$ -estradiol valerate from which estradiol is

formed after it is taken into the body, conjugate equine estrogens and phytoestrogens are suitable as natural estrogens in the combined preparation according to the invention. Advantageously 19-nortestosterone derivatives, such as desogestrel, dienogest, gestoden and levonorgestrel, and C-21 gestogens, such as medroxyprogesterone acetate, chlormadinone acetate and natural progesterone can be used as the gestogen.

The combination preparation of the invention especially includes combination preparations for oral administration, but also preparations for intravaginal and parenteral administration, in the form of a topical, rectal, intranasal, intrabuccal or sublingual administratable compositions.

The combination preparation according to the invention is prepared in a known manner in a suitable dosage with the conventional solid or liquid carrier materials or diluents and the conventionally used pharmaceutical auxiliary materials according to the desired manner of administration. Tablets, film tablets, pills or hard gelatin capsules may be used in oral administration.

In the combination preparation according to the invention the estrogen-gestogen balance is shifted largely in favor of the estrogen ingredient and in a predetermined stage the gestogen is completely eliminated from the daily dosage. Furthermore this regimen allows an extremely high

estrogen daily dosage (more than 4 mg estradiol equivalents/day). The shortening of the time intervals in which a daily dosage is not taken to 2 to 4 days increases both the cycle stability and also the contraceptive protection. The extension of the estrogen stage at the end of the gestogen stage for about 2 to 4 days has no influence on the standard occurrence of the end of bleeding but prevents the incipient follicle growth for the following cycle. The latter result was discovered in subsequent experiments with combinations of estradiol and dienogest. The size of the sonographically measured ovarian follicle never exceeded 10 mm.

The combination preparation according to the invention prevented the gestogen-induced activity of the enzymes, estradiol-17 $\beta$ -dehydrogenase and sulfotransferase, so that the conversion of natural estrogens like that of 17 $\beta$ -estradiol into the less effective estrone occurs to a lesser extent. Because of that sufficient estrogen action in the endometrium is guaranteed, also with natural estrogens. The combination preparation according to the invention has a high reliability as a contraceptive. Because of the use of natural estrogens an accumulation of xenobiotics in the body can be largely prevented by administration of the contraceptive. Natural estrogens also do not have carcinogenic activity.

The invention is now illustrated with a few examples. The improvement of the cyclic bleeding behavior in women is also proven.

### EXAMPLES

#### Example 1:

The following regimen was used for administration:

- 1 to 3 days: 3 mg estradiol valerate/day
- 4 to 7 days: 2 mg estradiol valerate/day +  
0.075 mg desogestrel/day
- 8 to 23 days: 2 mg estradiol valerate/day +  
0.150 mg desogestrel/day
- 24 to 25 days: 1 mg estradiol valerate/day
- 26 to 28 days: placebo

The studies were performed on 101 test subjects of ages from 18 to 25 years. The duration of administration amounted to 6 cycles. The average rate of intervening bleeding (bleeding discharge and spotting) dropped from 20.2 % in the first administration cycle to 10.7 % in the 6th cycle.

During the administration no unwanted pregnancy occurred.

The serum concentration of progesterone was measured radioimmunologically in 57 test subjects out of 101 on the eighth, twenty second and twenty fourth day of the cycle respectively. A limiting value of 4.0 ng/ml was measured in the fourth cycle during administration only in a few patients. All other measured values were clearly under 2

ng/ml. Thus the reliable ovulation inhibition could be documented using the preparation according to the invention.

Example 2:

The following regimen was used for administration:

- 1 to 3 days: 3 mg micronized  $17\beta$ -estradiol/day
- 4 to 7 days: 2 mg micronized  $17\beta$ -estradiol/day +  
0.075 mg desogestrel/day
- 8 to 23 days: 2 mg micronized  $17\beta$ -estradiol/day +  
0.150 mg desogestrel/day
- 24 to 25 days: 1 mg micronized  $17\beta$ -estradiol/day
- 26 to 28 days: placebo

In contrast to the first example micronized  $17\beta$ -estradiol was used instead of estradiol valerate. Analogous result to those in Example 1 were obtained in a smaller number of test subjects.

Example 3

The following regimen was used for administration:

- 1 to 3 days: 2.5 mg conjugated equine estrogen(CEE)/day
- 4 to 7 days: 1.25 mg CEE/day +  
1 mg dienogest/day
- 8 to 23 days: 1.25 mg CEE/day +  
2 mg dienogest/day
- 24 to 25 days: 0.60 mg CEE/ day
- 26 to 28 days: placebo

05648858-082500

In appropriate clinical studies 87 women of age 35 to 47 years were given the contraceptive preparation. The duration of administration amounted to 6 cycles. The intervening bleeding rate (discharge bleeding and spotting) was 15.7 % in the first cycle and continuously dropped to 7 % in the last cycle during administration. An oral glucose tolerance test was performed in an additional 17 women prior to the beginning of administration and at the end of the 6th cycle studied. In regard to the insulin concentration no variation from the normal range (2 to 25 mU/l) was observed. The insulin/glucose behavior was in the normal range in all test subjects at each measuring time point. The increase of C-peptides was significant. HbA1c shows a significant change between the control cycle and the 6 cycles during administration. The flat glucose values were significantly increased in comparison to the control at the conclusion of testing in 4 test subjects. In oral glucose tolerance tests only 3 test subjects had a reduced glucose tolerance. Two of these 3 test subjects were overweight. The results show that the contraceptive according to the invention based on natural estrogens had an excellent metabolic tolerance.

#### Example 4

The following regimen was used for administration:

- 1 to 3 days: 2.5 mg conjugated equine estrogen(CEE)/day
- 4 to 7 days: 1.25 mg CEE/day +  
150 mg micronized progesterone/day
- 8 to 23 days: 1.25 mg CEE/day +  
300 mg micronized progesterone/day
- 24 to 25 days: 0.60 mg CEE/ day
- 26 to 28 days: placebo

In this example micronized progesterone is used instead of dienogest as the gestogen component.

#### Example 5

The following regimen was used for administration:

- 1 to 3 days: 3 mg estradiol valerate/day
- 4 to 7 days: 1 mg estradiol valerate/day +  
1 mg dienogest/day + 0.010 mg ethinyl  
estradiol/day
- 8 to 23 days: 1 mg estradiol valerate/day +  
2 mg dienogest/day + 0.010 mg ethinyl  
estradiol/day
- 24 to 25 days: 1 mg estradiol valerate/day
- 26 to 28 days: placebo

In this fifth application example in contrast to the previous examples the entire 20 daily dosages were divided in the second and third stages and indeed in 1 mg natural estrogen complemented by 0.01 mg of synthetic estrogen. In the corresponding clinical studies this multistage



preparation was taken by 60 women of age from 18 to 40 years. The study parameters were reliability of contraceptive action (Pearl Index), cycle behavior and compatibility or tolerance. The results were complete suppression of follicle maturation (progesterone blood level determination, sonography) and an outstanding cycle control (intervening bleeding rate dropped from 12.1 % in the first cycle to 6 % in the final cycle during administration).

The results of these studies proved above all the outstanding good cycle stability of the regimen.

The invention described and claimed herein is also disclosed in German Patent Application 195 40 253.7-41 filed in Germany on October 28, 1995. Priority rights based on the aforesaid German Patent Application are being claimed. The disclosure in the priority document, German Patent Application 195 40 253.7-41, is incorporated in this specification by reference.

While the invention has been illustrated and described as embodied in a combination preparation for contraception based on natural estrogens, it is not intended to be limited to the details shown, since various modifications and changes may be made without departing in any way from the spirit of the present invention.

Without further analysis, the foregoing will so fully reveal the gist of the present invention that others can, by

applying current knowledge, readily adapt it for various applications without omitting features that, from the standpoint of prior art, fairly constitute essential characteristics of the generic or specific aspects of this invention.

What is claimed is new and is set forth in the following appended claims.

We Claim:

1. A combination preparation for contraception comprising from 2 to 4 first stage daily dosage portions each including an effective amount of at least one natural estrogen as sole active ingredient, from 16 to 22 second stage daily dosage portions each including an effective amount of a combination of at least one natural estrogen and at least one natural or synthetic gestogen as active ingredient; from 2 to 4 third stage daily dosage portions each including an effective amount of at least one natural estrogen as sole active ingredient; and from 2 to 4 additional stage daily dosage portions each containing a pharmaceutically acceptable placebo.

2. The combination preparation as defined in claim 1, wherein the 16 to 22 second stage daily dosage portions are divided into a first group of 3 to 5 of said daily dosage portions and a second group of 13 to 17 of said daily dosage portions and the amount of said at least one natural or synthetic gestogen in each of said daily dosage portions in said second group exceeds the amount of said at least one natural or synthetic gestogen in each of said daily dosage portions in said first group.

3. The combination preparation as defined in claim 1, wherein said at least one natural estrogen is selected from the group consisting of estradiol, estradiol compounds metabolized to said estradiol in the body, conjugated equine estrogens and phytoestrogens.

4. The combination preparation as defined in claim 1, wherein the at least one natural or synthetic gestogen is selected from the group consisting of natural progesterone and synthetic gestogens.

5. The combination preparation as defined in claim 4, wherein said synthetic gestogens include medroxyprogesterone acetate.

6. A method of contraceptive, said method of contraception comprising the steps of:

a) administering daily for 2 to 4 days an effective amount of at least one natural estrogen as sole active contraceptive ingredient in a first administration stage;

b) administering daily for 16 to 22 days an effective amount of a combination of at least one natural estrogen and at least one natural or synthetic gestogen as active contraceptive ingredient in a second administration stage;

c) administering daily for 2 to 4 days an effective amount of at least one natural estrogen as sole active contraceptive ingredient in a third administration stage; and

d) administering daily for 2 to 4 days a placebo in a fourth administration stage.

7. The method as defined in claim 6, wherein the at least one natural or synthetic gestogen is selected from the group consisting of natural progesterone and synthetic gestogens and the at least one natural estrogen is selected from the group consisting of estradiol, estradiol compounds metabolized to said estradiol in the body, conjugated equine estrogens and phytoestrogens.

#### ABSTRACT OF THE DISCLOSURE

The combination preparation for contraception includes from 2 to 4 first stage daily dosage portions each including an effective amount of at least one natural estrogen as sole active ingredient, from 16 to 22 second stage daily dosage portions each including an effective amount of a combination of at least one natural estrogen and at least one natural or synthetic gestogen as active ingredient; from 2 to 4 third stage daily dosage portions each including an effective amount of at least one natural estrogen as sole active ingredient; and from 2 to 4 final stage daily dosage portions containing a pharmaceutically acceptable placebo. The estrogen may be estradiol, an estradiol compound that is metabolized to estradiol when taken into the body, a conjugated equine estrogen or a phytoestrogen. The natural or synthetic gestogen can be natural progesterone or a synthetic gestogens, such as medroxyprogesterone acetate.

---

COMBINED DECLARATION AND POWER  
OF ATTORNEY

ATTORNEY DOCKET NO.

As a below-named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name,

I believe that I am an original, first and joint inventor of the subject matter which is claimed and for which a patent is sought on the invention entitled:

"Combination Compound for Contraception Based on Natural Estrogen"  
the specification of which:

(Check one) ☒ is attached hereto.

\_\_\_ was filed on \_\_\_\_\_ as

Application Serial No. \_\_\_\_\_ and

was amended on \_\_\_\_\_  
(if applicable)

was amended through \_\_\_\_\_  
(if applicable)

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to the examination of this application in accordance with Title 37, Code of Federal Regulations, Section 1.56(a).

I hereby claim foreign priority benefits under Title 35, United States Code, Section 119, of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed:

Prior Foreign Application(s):

Priority Claimed

195 40 253.7-41

Germany

October 28, 1995

x

\_\_\_\_\_  
Priority Number

\_\_\_\_\_  
Country

\_\_\_\_\_  
Date filed (Priority Date)

\_\_\_\_\_  
Yes

\_\_\_\_\_  
No

\_\_\_\_\_  
Priority Number

\_\_\_\_\_  
Country

\_\_\_\_\_  
Date filed (Priority Date)

\_\_\_\_\_  
Yes

\_\_\_\_\_  
No

\_\_\_\_\_  
Priority Number

\_\_\_\_\_  
Country

\_\_\_\_\_  
Date filed (Priority Date)

\_\_\_\_\_  
Yes

\_\_\_\_\_  
No

I hereby claim the benefit under Title 35, United States Code, Section 120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, Section 112, I acknowledge the duty to disclose material information as defined in Title 35, Code of Federal Regulations, Section 1.56(a), which occurred between the filing date of the prior application and the national or PCT International filing date of this application:

_____ (Application Serial No.)	_____ (Filing Date)	_____ (Status - Patented, pending, abandoned)
-----------------------------------	------------------------	--------------------------------------------------

_____ (Application Serial No.)	_____ (Filing Date)	_____ (Status - Patented, pending, abandoned)
-----------------------------------	------------------------	--------------------------------------------------

_____ (Application Serial No.)	_____ (Filing Date)	_____ (Status - Patented, pending, abandoned)
-----------------------------------	------------------------	--------------------------------------------------

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that those statements were made with the knowledge that wilful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such wilful false statements may jeopardize the validity of the application or any patent issued thereon.

The undersigned hereby authorizes **Michael J. Striker** and the firm of **Striker, Striker & Stenby**, to accept and follow instructions from:

Jenapharm GmbH, Otto-Schott-Strasse 15  
Jena, Germany D-07745

as to any action to be taken in the Patent and Trademark Office regarding this application without direct communication between Michael J. Striker, the firm of Striker, Striker & Stenby, and the undersigned. In the event of a change in the persons from whom instructions may be taken, Michael J. Striker and the firm of Striker, Striker & Stenby will be so notified by the undersigned.

I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith: \_\_\_\_\_

POWER OF ATTORNEY: Michael J. Striker, Registration No. 27233

Address all telephone calls to: Michael J. Striker

Telephone number: (212) 687 - 5068

Address all correspondence to: Striker, Striker & Stenby  
360 Lexington Avenue  
New York, New York 10017  
U.S.A.

005230 03384960



0054850 " 054960

FULL NAME OF SOLE OR FIRST INVENTOR: DITTGEN, Michael	INVENTOR'S SIGNATURE: <i>Michael Dittgen</i>	DATE: 23/9/96
RESIDENCE: Heidenberg 35/37 Apolda, Germany 99510		CITIZENSHIP: German
FULL NAME OF SECOND INVENTOR: FRICKE, Sabine	INVENTOR'S SIGNATURE: <i>Sabine Fricke</i>	DATE: 24/9/96
RESIDENCE: An der Riese 16 Jena, Germany 07749		CITIZENSHIP: German
FULL NAME OF THIRD INVENTOR: HOFFMANN, Herbert	INVENTOR'S SIGNATURE: <i>Herbert Hoffmann</i>	DATE: 23/9/96
RESIDENCE: Treunertstrasse 12 Jena, Germany 07749		CITIZENSHIP: German
FULL NAME OF FOURTH INVENTOR: MOORE, Claudia	INVENTOR'S SIGNATURE: <i>Claudia Moore</i>	DATE: 23/9/96
RESIDENCE: Novalisstrasse 23 Jena, Germany 07747		CITIZENSHIP German:
FULL NAME OF FIFTH INVENTOR: OETTEL, Michael	INVENTOR'S SIGNATURE: <i>Michael Oettel</i>	DATE: 29/9/96
RESIDENCE: Beethovenstrasse 30 Jena, Germany 07743		CITIZENSHIP: German
FULL NAME OF SIXTH INVENTOR: OSTERTAG, Monika	INVENTOR'S SIGNATURE: <i>Monika Ostertag</i>	DATE: 28/9/96
RESIDENCE: Haussenstrasse 14, Göttingen, Germany 37073		CITIZENSHIP: German

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In re:

Applicant : DITTGEN, M., ET AL  
Ser. No. : Continuation of 08/738,314  
Filed :  
Group No. :

**NOTIFICATION OF CHANGE OF ADDRESS  
OF APPLICANT'S ATTORNEY**

Honorable Commissioner  
of Patents and Trademarks  
Washington, D.C. 20231

Sir:

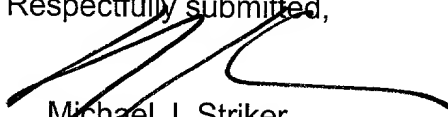
PLEASE TAKE NOTICE THAT, EFFECTIVE IMMEDIATELY, THE  
CORRESPONDENCE ADDRESS FOR THE ATTORNEY FOR THE APPLICANT HAS  
BEEN CHANGED AS FOLLOWS:

**STRIKER, STRIKER & STENBY  
103 EAST NECK ROAD  
HUNTINGTON, N.Y. 11743**

**TEL.: (631) 549 4700**

EFFECTIVE IMMEDIATELY, PLEASE DIRECT ALL  
CORRESPONDENCE TO THE ADDRESS SET FORTH ABOVE.

Respectfully submitted,



Michael J. Striker  
Reg. No. 27233

005330" 85884960